REMARKS

I. Status of Claims

Upon entry of this amendment, claims 1-8 and 11-19 are pending in the application. Claim 12 has been amended. Support for the amendment to claim 12 can be found, *inter alia*, in claim 12 as originally filed. The amendments introduce no new subject matter.

II. Claim Objections

Claim 12 is objected to because of the use of the acronym "OMV." Claim 12 has been amended to replace the abbreviation with "outer membrane vesicle." Therefore, applicants respectfully request that the objection be withdrawn.

III. Drawings

The drawings are objected to because Figure 3 contains sequences that have not been identified by sequence identifiers in the drawings or in the Brief Description of the Drawings.

The specification has been amended to include sequence identifiers in the Brief Description of the Drawings. Therefore, applicants respectfully request that the objection be withdrawn.

IV. Rejections under 35 U.S.C. § 102

Claims 1-3, 5-7, 11 and 12 are rejected under 35 U.S.C. § 102 as allegedly being unpatentable over Gorringe *et al.* (WO 01/73080) (Gorringe).

Applicants respectfully traverse the rejection and its supporting remarks.

A. Gorringe does not teach each and every element of the claimed invention

The legal standard for anticipation under 35 U.S.C. § 102 is one of strict identity. *Trintec Industries, Inc. v. Top-U.S.A. Corp.*, 63 U.S.P.Q.2d 1597 (Fed. Cir. 2002). To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention. *In re Paulson*,

30 F.3d 1475, 1478-79, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994) (citing *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990)) (emphasis added). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (emphasis added); MPEP §2131.

Gorringe fails to teach "an outer membrane vesicle (OMV) preparation from a bacterium, wherein … and the bacterium is *N. meningitidis* or *N. gonorrhoeae* …" The section of Gorringe cited by the Examiner, page 5, lines 30-37, teaches expression of the tbp from a pathogenic Neisseria "in a ***commensal*** Neisserial host". The section then goes on to suggest outer membrane vesicles from such host and indicates *N. lactamica*, a commensal Neisseria, is an exemplary host. Since the present claims are directed to OMVs from *N. meningitidis* or *N. gonorrhoeae*, which are pathogenic, i.e., not commensal, the Examiner has not established a *prima facie* case of anticipation.

Thus, Gorringe fails to anticipate for the exact same reasons that Robinson *et al.* failed to render the claims obvious as which resulted in the Examiner withdrawing the obviousness rejection in light of Robinson *et al.* Robinson *et al.*, taught expression in commensal neisserial strains specifically to avoid to toxicity and potential virulence issues, as such modifying Robinson *et al.* to use pathogenic strains would have rendered the compositions of Robinson *et al.* unsuitable for their intended purpose. Gorringe similarly teaches expression of the pathogenic Tbps in ***commensal neisserial*** hosts rather than a pathogenic neisserial host likely for the same reasons that Robinson *et al.* did. Thus Gorringe does not anticipate the pending claims and cannot be used in an obviousness rejection as a modification to use *N. meningitidis* or *N. gonorrhoeae* as is claimed would render the compositions of Gorringe unsuited for their intended purpose.

B. Gorringe does not teach the claimed invention because the limitations are not arranged or combined in the same way as recited in the claim

"[A]n invention is anticipated if the same device, including all the claim limitations, is shown in a single prior art reference. Every element of the claimed invention must be literally

present, arranged as in the claim. The identical invention must be shown in as complete detail as is contained in the patent claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) (emphasis added). "[U]nless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102." *Net MoneyIN, Inc. v. VeriSign, Inc.*, No. 2007-1565 at 17-18 (Fed. Cir. Oct. 20, 2008) (emphasis added).

In its recent *Net MoneyIN v. Verisign* decision, the Federal Circuit explained the meaning of the phrase "arranged as in the claim" as follows:

> The meaning of the expression "arranged as in the claim" is readily understood in relation to claims drawn to things such as ingredients mixed in some claimed order. In such instances, a reference that discloses all of the claimed ingredients, but not in the order claimed, would not anticipate, because the reference would be missing any disclosure of the limitations of the claimed invention "arranged as in the claim." But the "arranged as in the claim" requirement is not limited to such a narrow set of "order of limitations" claims. Rather, our precedent informs that the "arranged as in the claim" requirement applies to all claims and refers to the need for an anticipatory reference to show all of the limitations of the claims arranged or combined in the same way as recited in the claims, not merely in a particular order. The test is thus more accurately understood to mean "arranged or combined in the same way as in the claim."
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> *Net MoneyIN* at 15-16 (emphasis added).

Even if Gorringe, as alleged by the Examiner, teaches each and every limitations of the presently claimed invention, it is respectfully submitted that Gorringe discloses a completely different arrangement of the elements from the one presently claimed.

Gorringe discloses at least three embodiments two of which are related to one another. The main embodiment that Gorringe discloses and discusses in the majority of the specification is a non-neisserial cell expressing a neisserial iron uptake protein, wherein the iron uptake protein can be

extracted from the cell under mild conditions and while retaining substantially the antigenicity of native iron uptake protein (page 3, lines 9-12) (emphasis added). Gorringe defines "mild conditions" as conditions under which the "recombinant protein can be extracted without the need to denature and then renature the protein" (page 4, lines 25-26) and provides that an iron uptake protein "can easily be extracted using mild conditions, such as using a conventional detergent extraction method" (page 4, lines 20-21). Gorringe further states:

> The Tbp is suitably extracted by solubilising membrane associated Tbp in a non-ionic detergent solution, yielding good quantities of Tbp in native form and which has been demonstrated to be both functional and protective against meningococcal challenge. A number of non-ionic detergents are suitable for the extraction, including one chosen from an alkyl glucoside; *n*-octyl-β-D-glucopyranoside; TRITON® X100; ELUGENT®; dodecyl-maltoside; and *n*-octyl-β-D-maltoside (page 6, lines 1-7).

In an example illustrating the production of recombinant Tbp proteins, Gorringe provides that *E. Coli* strains containing Tbp gene inserts were grown up and harvested by centrifugation (page 11, lines 13-24). It further provides that crude membranes were prepared by disrupting cells with a bead-beater (page 12, line 27) which the Examiner has interpreted as meeting the limitation of "wherein the bacterial membrane is disrupted substantially in the absence of any detergent." Applicants respectfully submit that the Examiner has taken the passage on disrupting cells with a bead-beater out of context. After the cells were disrupted with a bead-beater, the membrane preparation was mixed with a buffer which contained 4% (v/v) Elugent™ detergent (page 12, lines 34-36).

The Examiner cited this process to support the assertion that Gorringe taught preparation of OMVs in the absence of any detergent. However, this process cited by the Examiner is on pages 12, line 15 through page 13, line 2, is clearly part of the embodiment directed to extraction and purification of the isolated Tbp, rather than preparation of OMVs. Further, the Examiner has not demonstrated that the bead-beater would have produced OMVs rather than randomly shredded membrane fragments (i.e., not intact vesicles) even if used on the non-pathogenic Neisseria

expressing the pathogenic Neisseria TbpA described on page 5, lines 35-37. In the purification procedure disclosed by Gorringe, the precipitate was collected after an 8000g centrifugation (page 12, lines 31-36), whereas in the purification procedure for OMVs disclosed in the presently claimed invention which is directed at purifying outer membrane vesicles, the precipitate after a 10,000g centrifugation was discarded (page 11, lines 4-5). Thus, in the Gorringe preparation, the Tbp was in the precipitate. If the bead-beater had produced OMVs, the Tbp would have been in the supernatant where the OMVs, if produced, would have been. This strongly suggests that the bead beater shreds the membrane into small fragments that precipitate rather then gently producing intact vesicles that float.

In contrast to the present invention, which recites a process for the manufacture of an OMV preparation from a bacterium, wherein the bacterial membrane is disrupted substantially in the absence of deoxycholate detergent to produce the OMV preparation and the bacterium is *N. meningitidis* or *N. gonorrhoeae* and overexpresses TbpA, relative to the corresponding wild-type strain, Gorringe discloses in the main embodiment a non-neisserial cell expressing a neisserial iron uptake protein, wherein the iron uptake protein can be extracted from the cell under mild conditions and retains substantially the antigenicity of native iron uptake protein (page 3, lines 9-12). For the production of Tbps, Gorringe provides recombinant expression of Tbps in a non-neisserial cell, wherein the Tbp can be extracted from the cell under mild conditions (page 3, lines 9-12). Accordingly, the method taught in Gorringe does not comprise the production of OMVs, or the use of *N. meningitidis* or *N. gonorrhoeae* bacterium that overexpresses TbpA. Rather, Gorringe teaches the purification of an iron uptake protein from a non-neisserial cell, not OMVs that include a substantial number of different outer membrane proteins from *N. meningitidis* or *N. gonorrhoeae* bacterium.

The Examiner also alleges that Gorringe discloses a process for the preparation of an OMV preparation which includes expressing recombinant neisserial TbpA (page 5, lines 30-37). Applicants respectfully submit that this disclosure is discussing the two other embodiments disclosed in Gorringe. The first embodiment is discussed in lines 30-35, which is similar to the

embodiment discussed above, i.e., expressing the Tbp protein in a heterologous host, in this case a commensal Neisserial host, and extracting under mild conditions. The second separate embodiment is discussed in lines 35-37, which is directed at a method of producing Tbp from a pathogenic Neisseria comprising expressing a gene encoding the Tbp in a ***commensal neisserial*** and generating an outer membrane vesicle preparation. This embodiment is distinct from either of the other embodiments discussed above, which are directed at a non-neisserial cell expressing a neisserial iron uptake protein, wherein the iron uptake protein can be extracted from the cell under mild conditions and retains substantially the antigenicity of native iron uptake protein or expression of a Tbp in a commensal Neisserial host and extracting under mild conditions. Extracting a protein such as Tbp or generating outer membrane vesicle preparation appears to be mutually exclusive and is taught that way in Gorringe. Thus, the elements are arranged differently in Gorringe compared to the presently claimed invention, and constitute a distinct invention.

Therefore, Gorringe only teaches recombinant expression of Tbps in a non-neisserial cell, wherein the Tbp can be extracted from the cell under mild conditions. It does not, however, teach the production of OMVs, or the use of *N. meningitidis* or *N. gonorrhoeae* bacterium that overexpresses TbpA. Even if we assume, arguendo, that Gorringe teaches all the elements of the present invention, it is easy to see that Gorringe discloses a technology that is conceptually distinct and has a completely different arrangement of the elements compared to the present invention.

Accordingly, it is respectfully submitted that the present invention is not anticipated by Gorringe and therefore this rejection under 35 U.S.C. § 102(e) may properly be withdrawn.

V. Rejections under 35 U.S.C. § 103

Claims 1-8, 11, 12 and 19 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Morein *et al.* (Analytical Biochemistry, 1994; 216: 47-51) (Morein) in view of Gorringe as applied to claims 1-3, 5-7, 11 and 12, and van der Ley *et al.* (Vaccine; 1995; 13(4): 401-407) (van der Ley) and further in view of Rosenqvist *et al.* (WO 01/91788) (Rosenqvist).

Applicants respectfully traverse this rejection for the following reasons.

To make a *prima facie* case of obviousness, the teachings of the prior art should have suggested the claimed subject matter to the person of ordinary skill in the art, and all the claim limitations must be taught or suggested in the references cited by the Examiner. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). To make a prima facie case of obviousness, "it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." *KSR Intl Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007). The initial burden to make a prima facie case of obviousness is on the Examiner. *In re Bell*, 991 F.2d 781, 783 (Fed. Cir. 1993).

The teachings of Gorringe have been discussed in detail above. As discussed above, Gorringe teaches generation of OMVs from commensal Neisseria strains. To render the pending claims obvious, one of skill in the art would have to replace the commensal Neisseria strains with a pathogenic Neisseria, either *N. meningitidis* or *N. gonorrhoeae*. However, as discussed above, for the same reasons one of skill in the art would not have been motivated to modify Robinson *et al.* that way, one of skill in the art would not be motivated to modify Gorringe that way. Specifically, as with Robinson *et al.*, such a modification would render the OMVs of Gorringe unsuitable for their intended purpose. The Examiner acknowledged that this argument in the previous response was correct and withdrew the rejection over Robinson *et al.* Therefore the Applicants respectfully request that the Examiner withdraw the pending rejection as well as the same argument applies equally as well.

In addition as discussed above, Gorringe does not teach that the bacterial membrane is disrupted substantially in the absence of deoxycholate detergent to produce the OMV preparation as recited in the presently claimed invention. Even if we assume, arguendo, that Gorringe teaches all the elements of the present invention, it is easy to see that Gorringe discloses a technology that is conceptually distinct and has a completely different arrangement of the elements compared to the present invention. The teachings of Morein, van der Ley and Rosenqvist do not cure the deficiency of Gorringe because neither of them teaches disrupting the bacterial membrane substantially in the absence of deoxycholate detergent.

Based on these arguments alone, the rejected claims are not obvious. However, even assuming arguendo that a *prima facie* case has been made, such a case can be rebutted by evidence of unexpected results and commercial success. The case law is clear that secondary considerations, where present, must be considered in determining obviousness. "Though no requirement for such results is present in the statute, evidence of unexpected results may be strong support for a conclusion of nonobviousness." *Lindemann v. American Hoist and Derrick Comp.*, 730 F.2d 1452, 1461 (Fed. Cir. 1984). Failure to consider objective evidence of nonobviousness, for example evidence of unexpected results, is error. Evidence of secondary considerations "can often serve as insurance against the insidious attraction of the siren hindsight when confronted with a difficult task of evaluating the prior art." *Gore & Associates, Inc. v. Garlock*, 721 F.2d 1540, 1553 (Fed. Cir. 1983).

As shown by the presently claimed invention, the disruption of bacterial membrane substantially in the absence of deoxycholate detergent has unexpected advantages over the prior art. The first table on page 10 of the specification shows that use of non-detergent to generate OMVs is superior versus use of detergent because the detergent removes important antigens from the resulting OMVs, such as NspA, 287, and 741. Retaining these antigens in the final OMV produces a superior vaccine, but none of the teachings of Morein, van der Ley or Rosenqvist recognizes this advantage.

In summary, it is abundantly clear that combining the teachings of the prior art references does not teach or suggest all the limitations of the presently claimed invention, or recognize the unexpected advantage of the presently claimed invention. Accordingly, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness, which can be rebutted by secondary considerations even established, and therefore this rejection under 35 U.S.C. § 103(a) may properly be withdrawn.

Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing **Docket No. 223002100800**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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